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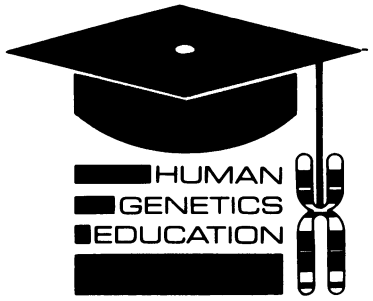
BIOGRAPHY
Profiles in Genetics: Archibald E. Garrod (1857–1936)



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Archibald Garrod, the father of "inborn errors of metabolism," was one of the great pioneers at the turn of the century and was far ahead of his time. He was a contemporary of William Bateson (a geneticist), John Scott Haldane (a physiologist), and F. Gowland Hopkins (a biochemist). The failure to follow Garrod's (1902, 1909) important discoveries remains one of the great mysteries of 20th-century science.

It is worthwhile to examine Garrod's intellectual background. His father, Alfred Baring Garrod, was a brilliant physician who obtained his medical degree at the age of 23 years, discovered the presence of uric acid in the blood of patients with gout, and was appointed professor of medicine at University College, London, when he was only 32 years old. Archibald Garrod's two older brothers also had brilliant academic careers. Following in their footsteps, Garrod not only met these high standards set by his father and brothers but easily exceeded their greatness, enjoying a more enduring career.

Garrod received a broad education, attending a preparatory school in Harrow and entering Marlborough at the age of 15 years. One frequent visitor to the Garrod household was his cousin, Charles Keene, an outstanding illustrator for the magazine *Punch* for over 40 years. At the age of 10 years, Archibald himself displayed his artistic talent by writing an illustrated booklet, *A Handbook of Classical Architecture.* He was keenly interested in natural history from an early age and displayed interest in what was later termed "genetics." As a tireless collector of butterflies at the age of 12 years, Garrod noted the dearth of females among the specimens collected. This is not usually due to a lopsided sex ratio but to the greater visibility and activity of the males of many species. His early writings contained references and speculations about the possible inheritance of certain characters in mammals.

It is of interest that Garrod's early performance at Marlborough was poor, largely because of his lack of interest in classical studies, especially Latin prose and grammar. However, with the encouragement of the master of his college, his performance improved, and he was able to enter Christ Church, Oxford. Garrod graduated in 1878, with a first in natural sciences. Following in his father's footsteps, in 1880, Garrod entered St. Bartholomew's Hospital in London, for his medical education. He won a number of scholarships, including the coveted Brackenbury Scholarship. Garrod qualified in 1884 and spent a year in Vienna attending the medical clinics, as was the custom in those days. One consequence of his visit was his very popular book on the laryngoscope (Garrod 1886). After joining his father's medical practice, he wrote a treatise on rheumatoid arthritis, in 1890.

Chemistry of Diseases

Garrod was appointed assistant physician at the Hospital for Sick Children on Great Ormond Street (London) in 1892, and for the rest of his life, he remained deeply interested in diseases of children. He was interested in studies of normal and pathological urine, especially in differences of their coloration. It is of interest that his interest in butterflies and flowers in childhood was also related to color differences and biological variation, and it may well have helped to sharpen his perception in this regard. It should be mentioned further that his work was greatly benefited from his close friendship with William Bateson, who advised him on the genetic aspects, and with F. Gowland

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Hopkins, who advised him on the chemistry of pigments. These two individuals were also responsible for profoundly influencing J. B. S. Haldane's work.

Garrod was greatly interested in both the etiological and the clinical aspects of alkaptonuria. Garrod's chemical studies established the true nature of the disease. He disproved the belief that alkaptonuria was infectious—i.e., attributable to microorganisms responsible for the formation of homogenistic acid in the gut, as had been believed—instead showing, because of its frequent occurrence in siblings, that it was congenital and possibly hereditary. These views were presented before the Medical and Chirurgical Society meeting in 1899. Gowland Hopkins was in the audience and vigorously supported Garrod in his commentary. In the following years, Garrod tirelessly emphasized the chemical individuality of each person, emphasizing its congenital and metabolic nature. Because of advice of William Bateson, Garrod came to appreciate the relationship between consanguinity and the recessive nature of the disease, in the families he studied. His classic paper on the genetics of alkaptonuria appeared in 1902 in *The Lancet* (Garrod 1902). In later years, Garrod regularly attended the meetings of the Genetical Society of Great Britain.

Inborn Errors of Metabolism

According to Graham (1936), the idea that alkaptonuria might be due to a chemical error in metabolism first occurred to Garrod one afternoon while he was walking home from the hospital to 9 Chandos Street in London. He thought of it at once as a congenital defect that persists throughout life. Later, in his lectures of 1903–4, Garrod extended his observations to a class of metabolic disorders that are congenital and lifelong.

Bearn (1976) noted that Garrod's friendship with F. Gowland Hopkins was critical to the investigation of the chemistry of diseases. In addition to alkaptonuria, Garrod (1909) dealt with a number of other disorders—such as albinism, cystinuria, porphyria, and pentosuria—calling them the "inborn errors of metabolism." However, Harris (1953) pointed out that not all of the conditions considered by Garrod can be regarded as "true" metabolic errors. For instance, in cystinuria, the excessive excretion of cystine and certain other amino acids may be due to a failure in renal tubular reabsorption, and it would be more correct to call it a renal anomaly rather than a metabolic one. However, Garrod's conclusions were essentially correct with respect to both the genetic basis of metabolic disorders and the gene-enzyme concept.

Garrod's Influence

Garrod's brilliant deductions might have ushered in the field of biochemical genetics. However, his work was largely ignored for many years, by both geneticists and biochemists, in spite of the support he enjoyed from Bateson and Hopkins. Several reasons have been advanced to explain this failure to follow up Garrod's pioneering work. Among the possible reasons are the following: (*a*) it was regarded as an *isolated* observation and not as the first of a series of complex metabolic disorders that were discovered many years later (Caspari 1968); (*b*) Garrod's approach combined the ideas and methods from a number of sources, such as genetics, biochemistry, and pathology, an approach that was not readily understood by most scientists of that time; and (*c*) the principles of genetics had not yet begun, and the term "genetics" itself was yet to be coined by Bateson. In the years following Garrod's work, biologists interested in genetic research were primarily interested in *Drosophila,* corn, and Oenothera. In the order of scientific developments, Garrod's discoveries were too early to be adequately appreciated and understood. Bearn and Miller (1979) speculated that physicians were not interested in such rare disorders as alkaptonuria, which they seldom encountered in their normal practices.

In 1920, Haldane discussed the gene-enzyme concept but attributed it to Cuenot (1903). It is hard to obtain Haldane's (1920) paper; but, it is included in a recent publication of his collected works (Dronamraju 1990, p. 542). During the 1920s and 1930s, research on the genetics of petal pigments was conducted, under Haldane's direction, by Scott-Moncrieff (1936, 1981) and colleagues at the John Innes Institution. In 1935, Beadle and Ephrussi adapted the transplantation technique (developed by Caspari [1933] for research on the mealmoth, *Ephestia kuhniella*) to *Drosophila.* Through their experiments involving reciprocal translocations of imaginal disks in *Drosophila,* Beadle and Ephrussi (1936) demonstrated the sequential chain of events in a normal metabolic chain. These studies paved the way to an understanding of mutant phenotypes.

Later, the genetic and biochemical investigation of Beadle and Tatum (1941), using *Neurospora,* led to the firm establishment of the principles of biochemical genetics. These studies were decisive in providing ex-

perimental proof for the genetic basis of biochemical phenomena. The convenience of using *Neurospora* mutants, which are haploid and are thus devoid of any complications of recessiveness and dominance, made it very easy to study the genetics of these mutants. Because the mutants are reparable, specific biochemical and genetic studies could be carried out. Tatum (1959) has summarized the essential findings of the work of Beadle and Tatum, as follows: (*a*) all biochemical processes in all organisms are under genetic control; (*b*) these biochemical processes are resolvable into series of individual stepwise reactions; (*c*) each biochemical reaction is under ultimate control of a different, single gene; and (*d*) mutation of a single gene results only in an alteration in the ability of the cell to carry out a single primary chemical reaction.

In a seminal paper, Haldane (1937) emphasized the genetic basis of chemical individuality, drawing attention to the pioneering work of Garrod (1902). Beadle (1967) wrote that he was not aware of Garrod's discoveries in biochemical genetics until after his own early work on *Neurospora* was completed (Beadle and Tatum 1941). He recorded that it was Haldane (1941) and Wright (1941) who first brought Garrod's work to his attention. However, Beadle was aware of Scott-Moncrieff's (1936) work on the genetics of anthocyanin pigments, which was carried out under Haldane's direction at the John Innes Institution in England. By the middle and late 1930s, the structure and variation of the main classes of pigments had been established, and genes controlling the relative amounts of the different pigments, the formation and inhibition of copigments, the state of oxidation and methylation of the pigments, and the pH of cell sap had been identified in several species. Further, identification of the enzymes and catalytic agents involved in the formation of the plant pigments was planned. However, these plans were interrupted by World War II; and, in the meantime, many of the questions raised by the work on plant pigments were answered by the work of Beadle and Tatum on *Neurospora* (Kay 1989).

In retrospect, how do we evaluate Garrod's place in the history of biochemical genetics? That he was a great pioneer who first formulated the gene-enzyme concept is not in doubt. However, Garrod's work exercised no influence in founding the gene-enzyme concept. By the time his work was rediscovered, its foundations had already been laid by the experiments of Beadle and Tatum (1941). Haldane (1954) wrote that he himself was partly responsible for the suggestion that a gene makes a particular species of enzyme or antigen (Haldane 1920); but, he was led to this hypothesis by Cuenot (1903) and not by Garrod. In his own time, Garrod's work was largely ignored by geneticists and physicians. It was Beadle and Tatum's experimental work that was mainly responsible for establishing biochemical genetics as a viable field (Dronamraju, in press).

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